

ALKYNYL-SUBSTITUTED SPIROCYClic SULFAMIDES FOR THE TREATMENT OF ALZHEIMER'S DISEASE

The present invention relates to a novel class of compounds, their salts, pharmaceutical compositions comprising them, processes for making them and their use in therapy of the human body. In particular, the 5 invention relates to compounds which modulate the processing of APP by γ -secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

Alzheimer's disease (AD) is the most prevalent form of dementia. Although primarily a disease of the elderly, affecting up to 10% of the 10 population over the age of 65, AD also affects significant numbers of younger patients with a genetic predisposition. It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain 15 regions of sufferers. These plaques mainly comprise fibrillar aggregates of β -amyloid peptide (A β), and although the exact role of the plaques in the onset and progress of AD is not fully understood, it is generally accepted that suppressing or attenuating the secretion of A β is a likely means of alleviating or preventing the condition. (See, for example, *ID research alert* 1996 1(2):1-7; *ID research alert* 1997 2(1):1-8; *Current Opinion in CPNS Investigational Drugs* 1999 1(3):327-332; and *Chemistry in Britain*, 20 Jan. 2000, 28-31.)

A β is a peptide comprising 39-43 amino acid residues, formed by proteolysis of the much larger amyloid precursor protein. The amyloid 25 precursor protein (APP or A β PP) has a receptor-like structure with a large ectodomain, a membrane spanning region and a short cytoplasmic tail. Different isoforms of APP result from the alternative splicing of three exons in a single gene and have 695, 751 and 770 amino acids respectively.

The A β domain encompasses parts of both extra-cellular and 30 transmembrane domains of APP, thus its release implies the existence of two distinct proteolytic events to generate its NH₂- and COOH-termini. At

least two secretory mechanisms exist which release APP from the membrane and generate the soluble, COOH-truncated forms of APP (APP_s). Proteases which release APP and its fragments from the membrane are termed "secretases". Most APP_s is released by a putative α -secretase which cleaves within the A β domain (between residues Lys¹⁶ and Leu¹⁷) to release α -APP_s and precludes the release of intact A β . A minor portion of APP_s is released by a β -secretase, which cleaves near the NH₂-terminus of A β and produces COOH-terminal fragments (CTFs) which contain the whole A β domain. Finding these fragments in the extracellular compartment suggests that another proteolytic activity (γ -secretase) exists under normal conditions which can generate the COOH-terminus of A β .

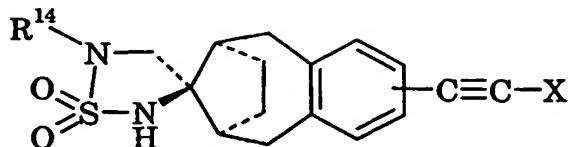
It is believed that γ -secretase itself depends for its activity on the presence of presenilin-1. In a manner that is not fully understood presenilin-1 appears to undergo autocleavage.

There are relatively few reports in the literature of compounds with inhibitory activity towards β - or γ -secretase, as measured in cell-based assays. These are reviewed in the articles referenced above. Many of the relevant compounds are peptides or peptide derivatives.

WO 01/70677 discloses certain sulphonamido-substituted bridged bicycloalkyl derivatives which are useful in the treatment of Alzheimer's disease, but neither discloses nor suggests the compounds of the present invention.

The present invention provides a novel class of non-peptidic compounds which are useful in the treatment or prevention of AD by modulating the processing of APP by the putative γ -secretase, thus arresting the production of A β and preventing the formation of insoluble plaques.

According to the invention there is provided a compound of formula I:



I

wherein X represents Ar, L-N(R¹)₂, L-CON(R¹)₂, L-CO₂R¹ or L-CN;

L represents a hydrocarbon chain of 1-7 carbon atoms which, when the chain comprises 2 or more carbon atoms, is optionally interrupted by
5 an oxygen atom;

R¹ represents H or R²; or two R¹ groups attached to a single nitrogen atom may complete a heterocyclic ring of 3-7 members bearing 0-3 substituents selected from halogen, oxo, NO₂, CN, CF₃, R², C₂₋₆acyl, C₂₋₆alkenyl, OH, OR², CO₂H, CO₂R², Ar, ArCH₂O, and ArO;

10 R² represents C₁₋₆alkyl which is optionally substituted with halogen, Ar, NO₂, CN, CF₃, OH or C₁₋₄alkoxy;

R¹⁴ represents H or C₁₋₆alkyl, C₃₋₇cycloalkyl, C₃₋₆cycloalkylC₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, phenyl or benzyl, any of which optionally bear up to 3 halogen substituents or one substituent selected from CN, NO₂, OH,
15 C₁₋₄alkoxy, CO₂H, C₁₋₄alkoxycarbonyl, C₂₋₆acyl, C₂₋₆acyloxy, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₂₋₆acylamino, carbamoyl, C₁₋₄alkylcarbamoyl and di(C₁₋₄alkyl)carbamoyl; and

Ar represents phenyl or heteroaryl either of which optionally bears up to 3 substituents independently selected from halogen, CF₃, NO₂, CN,
20 OCF₃, C₁₋₆alkyl and C₁₋₆alkoxy;

or a pharmaceutically acceptable salt thereof.

Where a variable occurs more than once in formula I or in a substituent thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified.

25 As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

Derived expressions such as "C₂-alkenyl", "hydroxyC₁-alkyl", "heteroarylC₁-alkyl", "C₂-alkynyl" and "C₁-alkoxy" are to be construed in an analogous manner. Most suitably, such groups comprise no more than 4 carbon atoms.

5 The expression "C₃-7cycloalkyl" as used herein refers to nonaromatic monocyclic or bicyclic hydrocarbon ring systems comprising from 3 to 7 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl and bicyclo[2.2.1]heptyl.

10 The expression "C₃-6 cycloalkyl(C₁-6)alkyl" as used herein includes cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

15 The expression "C₂-acyl" as used herein refers to (C₁-alkyl)carbonyl groups, such as acetyl, propanoyl and butanoyl, including cycloalkyl derivatives such as cyclopentanecarbonyl and cyclobutanecarbonyl and halogenated derivatives such as trifluoroacetyl.

20 The expression "heteroaryl" as used herein means a cyclic or polycyclic system of up to 10 ring atoms selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and comprises at least one ring atom which is other than carbon. Monocyclic systems comprising 5 or 6 ring atoms are preferred. Preferably not more than 3 ring atoms are other than carbon. Where a heteroaryl ring comprises two or more atoms which are not carbon, not more than one of said atoms may be other than nitrogen. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thieryl, pyrazolyl, 25 oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, triazolyl and thiadiazolyl groups and benzo-fused analogues thereof. Further examples of suitable heteroaryl ring systems include 1,2,4-triazine and 1,3,5-triazine.

30 The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

For use in medicine, the compounds of formula I may advantageously be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable 5 pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic 10 acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with 15 suitable organic ligands, e.g. quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be 20 understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

The compounds of formula I exist as two sets of positional isomers, depending on whether the alkynyl group is attached at an *ortho* position relative to the fused ring junction, or at a *meta* position relative to said 25 junction. *Meta* attachment is preferred. For each positional isomer, two enantiomeric forms are possible, depending on which of the two available *ortho* or two available *meta* positions is occupied. For each positional isomer, the invention extends to both enantiomers, as pure compounds or as enantiomeric mixtures in any proportion. Furthermore, structural 30 formulae depicting one enantiomeric form are to be construed as representing both enantiomeric forms, unless otherwise stated.

The compounds of formula I are alkynyl-substituted benzo-fused bridged bicycloalkane derivatives comprising a spiro-linked cyclic sulphamide moiety.

In the compounds of formula I, R¹⁴ preferably represents optionally substituted C₁₋₆alkyl (such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, sec-butyl, cyanomethyl, 2-fluoroethyl, methoxyethyl, trifluoromethyl and 2,2,2-trifluoroethyl), C₃₋₇cycloalkyl (such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl), C₃₋₆cycloalkylC₁₋₆alkyl (such as cyclopropylmethyl, cyclobutylmethyl and cyclopentylmethyl), C₂₋₆alkenyl (such as allyl), C₂₋₆alkynyl (such as propargyl), or optionally substituted phenyl or benzyl. R¹⁴ very aptly represents n-propyl or 2,2,2-trifluoroethyl, an in a particular embodiment R¹⁴ represents 2,2,2-trifluoroethyl.

In the compounds of formula I, X represents Ar, L-N(R¹)₂, L-CON(R¹)₂, L-CO₂R¹ or L-CN, where Ar, L, R¹ and R² are as defined previously.

In this context, Ar typically represents optionally-substituted phenyl or 6-membered heteroaryl, such as pyridyl, pyrimidinyl or pyrazinyl. Suitable substituents include halogen (especially F or Cl), trifluoromethyl and methyl. In a particular embodiment, X represents 2-pyridyl, 3-pyridyl or pyrazinyl.

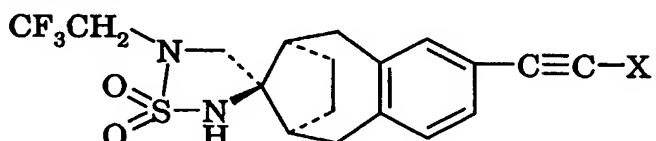
The linking group L represents a hydrocarbon chain comprising from 1 to 7 carbon atoms, optionally comprising an oxygen atom in the chain when 2 or more carbon atoms are present. Typically, L comprises from 1 to 6, preferably 1 to 5 carbon atoms. Suitable identities for L include -CH₂-, -(CH₂)₄-, -(CH₂)₅-, -(CH₂)₂-O-(CH₂)₂- and -(CH₂)₂-O-CH₂-.

R¹ represents H or R² where R² represents C₁₋₆alkyl which is optionally substituted with halogen, Ar, NO₂, CN, CF₃, OH or C₁₋₄alkoxy; or two R¹ groups attached to a single nitrogen atom may complete a heterocyclic ring of 3-7 members, optionally substituted as defined previously. Examples of groups represented by R¹ include H, methyl,

ethyl, propyl, butyl, benzyl, hydroxyethyl and methoxyethyl. When two R¹ groups combine to form a heterocyclic ring, suitable rings include pyrrolidine, piperidine, tetrahydropyridine, piperazine, morpholine, thiomorpholine and 2,5-diazabicyclo[2.2.1]heptane. Preferred ring 5 substituents include halogen, OH, oxo and R² groups (such as methyl, ethyl, propyl, hydroxymethyl and methoxymethyl), trifluoromethyl, acetyl, trifluoroacetyl, methoxycarbonyl, phenoxyethyl, pyridyl and phenyl, wherein the pyridyl and phenyl groups optionally bear up to 2 substituents selected from halogen (especially chlorine or fluorine), 10 C₁-alkyl and C₁-alkoxy. Examples of groups represented by N(R¹)₂ include benzylamino, N,N-dimethylamino, piperidin-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl, 4-phenylpiperazin-1-yl, N-(2-methoxyethyl)-N-methylamino, 4-trifluoromethylpiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 5-aza-2-oxabicyclo[2.2.1]hept-5-yl, 1,2,3,6-tetrahydropyridin-1-yl, N-(pyridin-15 2-ylmethyl)amino, N,N-bis(2-methoxyethyl)amino, 3,3-difluoropyrrolidin-1-yl, 4-hydroxy-4-trifluoromethylpiperidin-1-yl, 3-oxopiperazin-1-yl, 3-oxo-4-phenylpiperazin-1-yl, 4-methylpiperidin-1-yl, N-(2,2,2-trifluoroethyl)amino, N-(thiophene-2-ylmethyl)amino, 2-phenoxyethylmorpholin-4-yl, 3-(pyridin-3-yl)-pyrrolidin-1-yl, N-(4-20 phenylmorpholin-2-ylmethyl)amino and 3-hydroxypiperidin-1-yl.

Particular groups represented by N(R¹)₂ include benzylamino and 4-trifluoromethylpiperidin-1-yl.

A preferred subclass of the compounds of formula I are in accordance with formula II:



where X is as defined previously.

In one embodiment of this subset, X is selected from 6-membered heteroaryl, -CH₂N(R¹)₂, -(CH₂)₅N(R¹)₂, -(CH₂)₄CON(R¹)₂, -(CH₂)₄CO₂R², -(CH₂)₂-O-CH₂CN and -(CH₂)₂-O-(CH₂)₂N(R¹)₂.

Particular compounds in accordance with formula II include those
5 in which X represents 2-pyridyl, 3-pyridyl, pyrazinyl, 4-trifluoropiperidin-1-ylmethyl, -(CH₂)₅NH-CH₂Ph, -(CH₂)₄CONHCH₂Ph, -(CH₂)₄CO₂H, -(CH₂)₂-O-CH₂CN and -(CH₂)₂-O-(CH₂)₂NH₂.

The compounds of the present invention have an activity as inhibitors of γ secretase.

10 The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional
15 tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums or surfactants such as sorbitan monooleate, polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the
20 present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.
25 This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of
30

the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the
5 advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the
10 duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The present invention also provides a compound of the invention or
15 a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β -amyloid. Preferably the condition is a neurological disease having associated β -amyloid deposition such as Alzheimer's disease.

20 The present invention further provides the use of a compound of the present invention or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

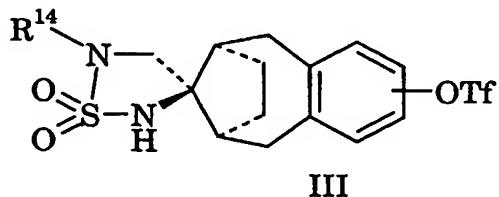
Also disclosed is a method of treatment of a subject suffering from or
25 prone to Alzheimer's disease which comprises administering to that subject an effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection
30 include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed

oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, 5 methylcellulose, poly(vinylpyrrolidone) or gelatin.

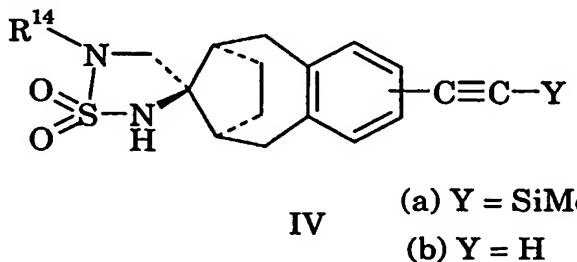
For treating or preventing Alzheimer's Disease, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, and especially about 0.01 to 5 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per 10 day. In some cases, however, dosage outside these limits may be used.

The compounds of formula I may be prepared by reaction of triflates III with alkynes $\text{HC}\equiv\text{C-X}$:



where Tf represents trifluoromethanesulphonyl (triflyl) and X and R^{14} have the same meanings as before. The reaction is typically carried out at elevated temperature (e.g. 90 – 150°C) under nitrogen in a sealed container in the presence of $(\text{Ph}_3\text{P})_4\text{Pd}(0)$, copper iodide, an amine and a solvent such as dioxan. Microwave heating may be employed.

Alternatively, the triflates III may be reacted with 20 trimethylsilylacetylene under similar conditions to provide alkynes IV(a):



where R^{14} has the same meaning as before. Hydrolysis of IV(a) (e.g. with LiOH in aqueous THF) provides acetylenes IV(b), which react with compounds X-G, where G is a suitable leaving group such as halogen

(especially Br or I) and X has the same meaning as before, to provide compounds of formula I. The reaction takes place in the presence of $(Ph_3P)_4Pd(0)$, copper iodide and an amine as before, and this route is particularly suitable when X represents Ar.

5 Individual compounds in accordance with formula I may be converted to different compounds in accordance with formula I by application of known synthetic techniques. For example, compounds of formula I in which X represents L-CN may be hydrolysed to the corresponding compounds in which X represents L-CO₂H, or reduced to the
10 corresponding compounds in which X represents L-CH₂NH₂. Similarly, compounds of formula I in which X represents L-CO₂H may be coupled with R²OH or (R¹)₂NH to provide the corresponding esters or amides wherein X represents, respectively, L-CO₂R² or L-CON(R¹)₂. Furthermore, compounds of formula I in which X represents L-CON(R¹)₂ may be reduced
15 to the corresponding amines in which X represents L-CH₂N(R¹)₂.

Where they are not commercially available, the above-mentioned reagents may be prepared by conventional routes. The synthesis of triflate III in which R¹⁴ represents 2,2,2-trifluoroethyl is described in the Examples, and analogous routes may be followed for other identities of
20 R¹⁴.

Where more than one isomer can be obtained from the above-described reaction schemes, then the resulting mixture of isomers can be separated by conventional means.

Where the above-described processes for the preparation of the
25 compounds according to the invention gives rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds
30 may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of

diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base.

5 The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional 10 protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

15 A typical assay which can be used to determine the level of activity of compounds of the present invention is as follows:

(1) Mouse neuroblastoma neuro 2a cells expressing human app695 are cultured at 50-70% confluence in the presence of sterile 10mM sodium butyrate.

20 (2) Cells are placed in 96-well plates at 30,000/well/100 μ L in minimal essential medium (MEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine, 0.2mg/ml G418 antibiotic, 10mM sodium butyrate.

(3) Make dilutions of the compound plate. Dilute stock solution to 5.5% 25 DMSO/110 μ M compound. Mix compounds vigorously and store at 4°C until use.

(4) Add 10 μ L compound/well. Mix plate briefly, and leave for 18h in 37°C incubator.

(5) Remove 90 μ L of culture supernatant and dilute 1:1 with ice-cold 30 25mM HEPES (pH.3), 0.1% BSA, 1.0mM EDTA (+ broad spectrum

protease inhibitor cocktail; pre-aliquotted into a 96-well plate). Mix and keep on ice or freeze at -80°C.

(6) Add back 100µL of warm MEM + 10% FBS, 50mM HEPES (pH7.3), 1% glutamine, 0.2mg/ml G418, 10mM sodium butyrate to each well, and
5 return plate to 37°C incubator.

(7) Prepare reagents necessary to determine amyloid peptide levels, for example by ELISA assay.

(8) To determine if compounds are cytotoxic, cell viability following compound administration is assessed by the use of redox dye reduction. A
10 typical example is a combination of redox dye MTS (Promega) and the electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.

(9) Quantitate amyloid beta 40 and 42 peptides using an appropriate volume of diluted culture medium by standard ELISA techniques.

15 (10) Add 15µL/well MTS/PES solution to the cells; mix and leave at 37°C.

(11) Read plate when the absorbance values are approximately 1.0 (mix briefly before reading to disperse the reduced formazan product).

20 Alternative assays are described in *Biochemistry*, 2000, 39(30), 8698-8704.

The Examples of the present invention all had an ED₅₀ of less than 100nM, typically less than 50nM and in most cases less than 10nM in at least one of the above assays.

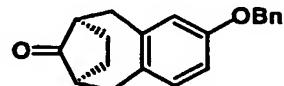
The following examples illustrate the present invention.

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EXAMPLES

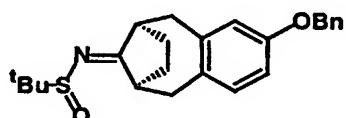
Intermediate 1

Step 1



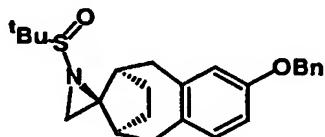
A mixture of 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-one (15 g; J. Org. Chem 1982, 47, 4329), K₂CO₃ (20.5 g) and benzyl bromide (10.6 ml) in DMF (100 ml) was stirred for 48 hrs at room temperature. The reaction was diluted with water (500 ml) and extracted with EtOAc (3x 150 ml). The combined organic phases were washed with water (2x 300 ml), brine (150 ml), dried and concentrated to give a gummy oil which crystallized on standing and after trituration with ether the title benzyl ether (19.5 g, 90%) as a white solid (360MHz ¹H, δ-CDCl₃) 1.32 (2H, m), 1.85 (2H, m), 2.57 (2H, m), 2.87 (4H, m), 5.05 (2H, s), 6.82 (2H, m), 7.11 (1H, d, J=8.2), 7.37 (5H, m).

Step 2



A solution of the product from Step 1 (20 g, 68 mmol), (+/-)-tert-butyl sulfinamide (9.2 g, 76 mmol) and titanium (IV) ethoxide (tech., 29.2 mL, 140 mmol) in dry THF (140 mL) was stirred and heated at reflux under nitrogen for 4 hours. The reaction was allowed to cool to room temperature and poured into rapidly stirred brine (160 mL). The mixture was stirred for 20 minutes, then filtered through Hyflo®, washing with ethyl acetate. The filtrate was transferred to a separating funnel. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x1). The combined organic extracts were washed with brine, then dried (Na₂SO₄), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 20→30% ethyl acetate / hexanes, to give the imine (24.9 g, 93%) as a colourless solid. MS(ES+) 396, MH⁺.

Step 3



Sodium hydride (60% dispersion in oil, 3.8 g, 95 mmol) was added portionwise to a stirred suspension of trimethyl sulfoxonium iodide (21 g,

95 mmol) in dry DMSO (150 mL) at room temperature under nitrogen.

After 90 minutes at room temperature, a solution of the product from Step

2 (24.9 g, 95 mmol) in dry DMSO (250 mL) was added such that the

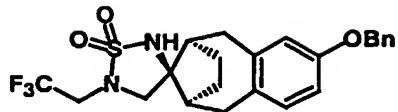
internal temperature remained below 30°C. The mixture was stirred at

- 5 room temperature for 4 hours, then quenched with water (1 L). The precipitate was collected by filtration. The solid was taken up in dichloromethane and washed with brine. The organic layer was dried (Na₂SO₄), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5→10% ethyl acetate / dichloromethane, to give the aziridine (23.2 g, 90%) as a colourless solid.
- 10 MS(ES+) 410, MH⁺.

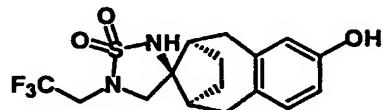
Step 4



- Trifluoroethyl amine (70 mL, 880 mmol) was added to a stirred suspension of the product from Step 3 (68.4 g, 167 mmol) and anhydrous zinc iodide (54 g, 170 mmol) in dry 1,2-dichloroethane (300 mL) at room temperature under nitrogen. The resulting solution was heated at 75°C, protected from light for 24 hours, an additional portion of trifluoroethyl amine (70 mL, 880 mmol) added and the reaction maintained at 75°C for a further 16 hours. The reaction was allowed to cool, then diluted with dichloromethane (500 mL) and water (400 mL). Sufficient sodium carbonate was then added to adjust the aqueous layer to ~pH 11. The small amount of precipitate was removed by filtration through Hyflo®. The layers were separated and the aqueous layer was extracted with dichloromethane (x3). The combined organic extracts were dried (Na₂SO₄), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5→10% ethyl acetate / dichloromethane, then with 10→20% methanol / dichloromethane, to give the diamine (59.6g, 88%) as a thick oil. MS(ES+) 405, MH⁺.

Step 5

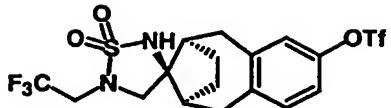
A solution of the product from Step 4 (59.6 g, 147 mmol) and sulfamide (42.5g, 442 mmol) in dry pyridine (350 mL) was stirred and heated at reflux under nitrogen for 4 hours. The reaction was allowed to cool, then the pyridine was removed in vacuo. The residue was azeotroped with toluene (x2) and the residue partitioned between dichloromethane (400 mL) and 1N hydrochloric acid (400 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica, eluting with dichloromethane, then 1→2→4% ethyl acetate / dichloromethane to give the cyclic sulfamide (53 g, 80%) as a colourless solid. ^1H NMR (360MHz, CDCl_3) δ_{H} 1.34 (2H, m), 1.70 (2H, m), 2.41 (2H, m), 2.62 (2H, m), 3.11 (2H, d, J =15.9), 3.20 (1H, d, J =15.9), 3.42 (2H, ABq, J =9.3, 13.3), 3.67 (2H, dq, J =2.2, 8.7), 4.76 (1H, s), 5.02 (2H, s), 6.72 (2H, m), 6.99 (1H, d, J =7.8), 7.37 (5H, m).

Step 6

A solution of the product from Step 5 (3.9g, 8.4 mmol) in methanol/ethyl acetate (4:1, 150 mL) was hydrogenated at 35 psi over 10% palladium on carbon (500 mg) for 4 hours at room temperature. The catalyst was removed by filtration through Hyflo®. The filtrate was evaporated, and the residue was purified by filtration through a pad of silica, eluting with 50% ethyl acetate/dichloromethane to give the phenol (3.2g) colourless solid. ^1H NMR (360MHz, $d_6\text{-DMSO}$) δ_{H} 1.06 (2H, m), 1.65 (2H, m), 2.29 (2H, m), 2.42 (2H, m), 3.04 (1H, d, J =15.6), 3.11 (1H, d,

J=15.6), 3.43 (2H, s), 3.99 (2H, brq, *J*=9.6), 6.47 (2H, m), 6.85 (1H, d, *J*=8), 7.93 (1H, s), 9.02 (1H, s).

Step 7

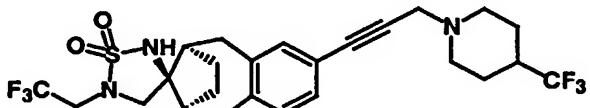


5 Pyridine (2.1 mL, 26 mmol) was added dropwise to a stirred solution/ suspension of the product from Step 6 (7.7g, 20 mmol) and triflic anhydride (4.3 mL, 25.6 mmol) in dry dichloromethane (200 mL) at 0°C under nitrogen. The cooling bath was removed and the reaction was stirred at room temperature for 4 hours. Water (300 mL) was added and 10 the layers were separated. The aqueous layer was extracted with dichloromethane (x2). The combined extracts were washed with brine (x1), then dried (Na_2SO_4), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5% ethyl acetate / dichloromethane, to give the triflate (6.7g, 65%) as an off white solid. ^1H NMR (360MHz, d_6 -DMSO) δ 0.99 (2H, m), 1.71 (2H, m), 2.38 (2H, brm), 2.69 (2H, m), 3.16 (1H, d, *J*=15.7), 3.18 (1H, d, *J*=15.7), 3.46 (2H, s), 4.02 (2H, brq, *J*=9.6), 7.18-7.31 (3H, m), 8.04 (1H, s).

15

Example 1

20



Step 1

25 4-Trifluoromethylpiperidine (2.0 g, 13 mmol) was added to a solution of propargyl bromide (80 wt.% 5.4 g, 36 mmol) in ethanol (30 ml). Potassium carbonate (5.4 g, 39 mmol) was added and the mixture was stirred at room temperature for 20 hours. The mixture was filtered and the solids washed with ethyl acetate. The filtrate was evaporated *in vacuo*, diluted with sodium hydrogen carbonate (sat, 50 ml) and extracted with ethyl acetate (2 x 40 ml). The extracts were washed with brine, dried

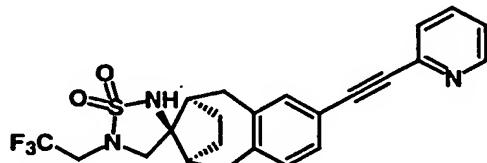
(MgSO₄) and evaporated *in vacuo* to provide 1-propargyl-4-trifluoromethylpiperidine as a brown oil (795 mg, 32%). (ES+) 192 ([MH]⁺).

Step 2

- 5 A mixture of Intermediate 1 (200mg, 0.39mmol), the product from Step 1 (148 mg, 0.78mmol), tetrakis-triphenylphosphine palladium(0) (23mg, 5mol%), triphenyl phosphine (10mg, 10mol%) and copper iodide (7.6mg, 10mol%) in piperidine (2ml), in a crimp-top microwave vial, was sealed, purged with nitrogen and then irradiated in the Smith Synthesizer
- 10 Microwave to 150°C for 15 minutes. The reaction was diluted with sodium hydrogen carbonate (sat, 25 ml) and extracted with ethyl acetate (2 x 25 ml). The extracts were washed with water (10 ml) and brine, dried (MgSO₄) and evaporated *in vacuo* to a brown gum, which was purified by flash column chromatography on silica eluting with 20 to 30% EtOAc in
- 15 isohexane to give a beige gum. The gum was further purified by preparative TLC on silica eluting with 20% EtOAc in isohexane to give the title compound as a white solid (42mg, 20%). δ (¹H, 400 MHz, CDCl₃) 1.24-1.35 (2H, m), 1.64-1.75 (4H, m), 1.88-1.92 (2H, m), 1.99-2.08 (1H, m), 2.25 (2H, dd, J = 11.7 & 2.1 Hz), 2.42-2.46 (2H, m), 2.57-2.72 (2H, m), 3.03-3.06 (2H, m), 3.18 (2H, dd, J = 16.0 & 7.4 Hz), 3.43 (2H, s), 3.52 (2H, s), 3.64-3.70 (2H, m), 4.68 (1H, brS), 7.03 (1 H, d, J = 7.8 Hz) and 7.18-7.20 (2 H, m). (ES+) 550 ([MH]⁺).

Example 2

25



Step 1

- A solution of Intermediate 1 (200mg, 0.39mmol), trimethylsilylacetylene (112 µl, 0.78mmol), tetrakis-triphenylphosphine palladium(0) (20mg, 5mol%), triphenyl phosphine (10mg, 10mol%) and

copper iodide (7.6mg, 10mol%) was made up in 2ml of dry piperidine and added to a crimp top microwave vial. The vial was sealed, purged with nitrogen and then irradiated in the Smith Synthesizer Microwave to 150°C for 10 minutes. The reaction was diluted with EtOAc (100ml) and the
5 mixture washed successively with dilute NaHCO₃, 1M HCl solution and then saturated brine solution. The organic layer was then separated, dried (MgSO₄) and evaporated *in vacuo* giving a crude residue which was purified by flash column chromatography using 25% EtOAc in isohexane as eluant to give the trimethylsilylethynyl derivative as a white solid
10 (156mg, 86% yield). δ (¹H, 400 MHz, CDCl₃) 0.23 (9H, s), 1.25-1.30 (2H, m), 1.68-1.72 (2H, m), 2.42-2.45 (2H, m), 2.62-2.71 (2H, m), 3.15-3.22 (2H, m), 3.42 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 4.68 (1H, brs), 7.03 (1 H, d, J = 8.2Hz) and 7.22-7.24 (2 H, m).

Step 2

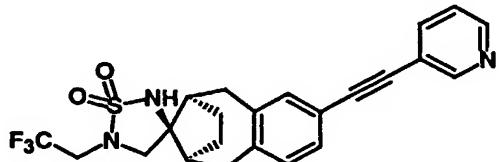
15 A solution of the product of Step 1 (156mg, 0.34mmol) in a 10:1 tetrahydrofuran/water mixture (10ml) was treated with lithium hydroxide (41mg, 1.71mmol) and stirred at room temperature for 1.5 hours. The reaction mixture was diluted with 50ml dichloromethane and washed with saturated brine solution. The organic phase was dried (MgSO₄) and
20 evaporated to dryness before purification by flash column chromatography using 20% ethyl acetate in isohexane as eluant to give the ethynyl derivative as a colourless film (86mg, 66%). δ (¹H, 400 MHz, CDCl₃) 1.28-1.32 (2H, m), 1.68-1.72 (2H, m), 2.42-2.46 (2H, m), 2.62-2.71 (2H, m), 3.05 (1H, s), 3.15-3.22 (2H, m), 3.43 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 4.66 (1H, brs), 7.03 (1 H, d, J = 8.2Hz) and 7.22-7.24 (2 H, m).

Step 3

A mixture of the acetylene derivative from Step 2 (32.5mg, 0.085mmol), 2-bromopyridine (20mg, 0.127mmol), tetrakis-
30 triphenylphosphine palladium(0) (8mg, 10mol%), triphenyl phosphine (2mg, 10mol%) and copper iodide (1.7mg, 10mol%) in dry piperidine (2ml) was added to a crimp top microwave vial, which was then sealed, purged with

nitrogen and irradiated in the Smith Synthesizer Microwave to 140°C for 10 minutes. After this time the reaction was diluted with EtOAc (30ml) and the mixture washed successively with dilute NaHCO₃, 1M HCl solution and then saturated brine solution. The organic layer was 5 separated, dried (MgSO₄) and evaporated *in vacuo*, giving a crude residue which was taken up in 1ml DMSO and purified by mass directed HPLC. δ (¹H, 400 MHz, CDCl₃) 1.26-1.35 (2H, m), 1.71-1.75 (2H, m), 2.47 (2H, m), 2.65-2.75 (2H, m), 3.12-3.22 (2H, dd), 3.43 (2H,s), 3.65-3.71 (2H, q), 4.8 (1H, brs), 7.1 (1H, m), 7.37-7.40 (2H, m), 7.42-7.47 (1H, m), 7.59-7.62 (1H, 10 m), 7.88-7.93 (1H, m), 8.72 (1H, m). (ES+) 462 ([MH]⁺).

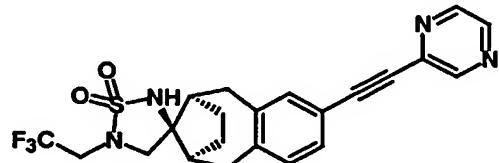
Example 3



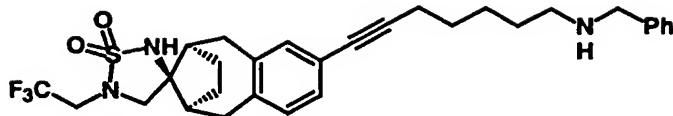
15 Prepared as in Example 2, using 3-bromopyridine in Step 3. δ (¹H, 400 MHz, CDCl₃) 1.26-1.35 (2H, m), 1.71-1.75 (2H, m), 2.47 (2H, m), 2.65-2.75 (2H, m), 3.12-3.22 (2H, dd), 3.43 (2H,s), 3.65-3.71 (2H, q), 4.68 (1H, brs), 7.1 (1H, m), 7.31-7.33 (2H, m), 7.48-7.51 (1H, m), 7.90-8.02 (1H, m), 8.60-8.62 (1H, m), 8.82 (1H, s). (ES+) 462 ([MH]⁺).

20

Example 4



Prepared as in Example 2, using iodopyrazine in Step 3. δ (¹H, 400 MHz, CDCl₃) 1.31-1.34 (2H, m), 1.72-1.76 (2H, m), 2.46-2.49 (2H, m), 2.68-2.77 (2H, m), 3.21-3.27 (2H, dd), 3.44 (2H, s), 3.65-3.71 (2H, q), 4.71 (1H, brs), 7.12-7.14 (1H, d), 7.38-7.39 (2H, m), 8.48 (1H, d), 8.57 (1H, m), 8.74 (1H, s). (ES+) 463 ([MH]⁺).

Example 55 **Step 1**

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (3.3 g, 17.4 mmol) was added to a mixture of 6-heptynoic acid (1.1 g, 8.7 mmol), benzylamine (950 μl , 8.7 mmol), 1-hydroxybenzotriazole (1.2 g, 8.7 mmol) and triethylamine (2.4 ml, 17.4 mmol) in tetrahydrofuran (25 ml) and the mixture was stirred at room temperature for 16 hours. The reaction was diluted with sodium hydrogen carbonate (sat, 60 ml) and extracted with ethyl acetate (2 x 100 ml). The extracts were washed with brine, dried (MgSO_4) and evaporated *in vacuo* to provide 6-heptynoic acid N-benzylamide as a brown solid (2.1 g, 99%). (ES+) 216 ([MH] $^+$).

15 **Step 2**

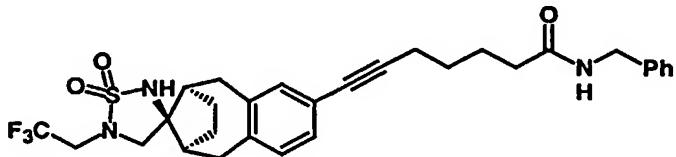
Lithium aluminium hydride (1m in THF, 10 ml, 10 mmol) was added to a solution of the amide from Step 1 (1.0 g, 4 .6 mmol) in THF (20 ml) and the mixture was heated at reflux for 16 hours. The reaction was cooled in ice and treated successively with water (0.4 ml), sodium hydroxide (0.4 ml) and water (1.2 ml) allowing 10 minutes between additions. The mixture was filtered through a bed of Celite® and washed through with THF. The filtrate was evaporated *in vacuo* to provide 7-(N-benzylamino)hept-1-yne as a yellow oil (924 mg, 99%). (ES+) 202 ([MH] $^+$).

Step 3

25 A mixture of Intermediate 1 (300 mg, 0.6 mmol), the alkyne from Step 2) (482 mg, 2.4 mmol), tetrakis-triphenylphosphine palladium(0) (35mg, 5 mol%), triphenyl phosphine (16mg, 10 mol%) and copper iodide (12 mg, 10 mol%) in triethylamine (5ml) in a sealed tube was purged with nitrogen and then heated at 90°C for 16 hours. The reaction was diluted with sodium hydrogen carbonate (sat, 30 ml) and extracted with ethyl

acetate (2 x 20 ml). The extracts were washed with water (x 3) and brine, dried (MgSO_4) and evaporated *in vacuo* to a dark oil, which was purified by flash column chromatography on silica eluting with DCM:MeOH:NH₃(aq) (120:8:1) to give a brown gum. The gum was further 5 purified flash column chromatography on silica eluting with EtOAc in isohexane (50% + 1% NH₃(aq)) to give the title compound as a clear foam (241mg, 72%). δ (¹H, 400 MHz, CDCl₃) 1.28-1.32 (2H, m), 1.45-1.71 (8H, m), 2.38-2.44 (4H, m), 2.60-2.70 (4H, m), 3.16 (2H, dd, J = 16.0 & 10.1 Hz), 3.42 (2H, s), 3.67 (2H, q, J = 8.6 Hz), 3.79 (2H, s), 7.00 (1 H, d, J = 7.8 Hz), 10 7.13-7.16 (2H, m), and 7.22-7.32 (4 H, m). (ES+) 560 ([MH]⁺).

Example 6

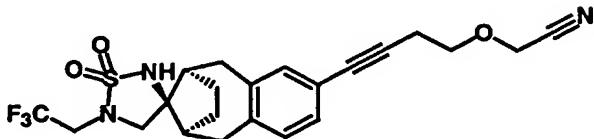


15 Step 1

A mixture of Intermediate 1, (150 mg, 0.3 mmol), the amide from Example 5, Step 1 (258 mg, 1.2 mmol), tetrakis-triphenylphosphine palladium(0) (17 mg, 5 mol%), triphenyl phosphine (8.6mg, 10 mol%) and copper iodide (6 mg, 10 mol%) in triethylamine (4 ml) in a sealed tube, was 20 purged with nitrogen and then heated at 100°C for 16 hours. Dioxane (4 ml) and tetrakis-triphenylphosphine palladium(0) (17 mg, 5 mol%), triphenyl phosphine (8.6mg, 10 mol%) and copper iodide (6 mg, 10 mol%) were added and the reaction was heated at 100°C for 16 hours. The reaction was diluted with sodium hydrogen carbonate (sat, 30 ml) and 25 extracted with ethyl acetate (2 x 20 ml). The extracts were washed with water (x 3) and brine, dried (MgSO_4) and evaporated *in vacuo* to a brown gum, which was purified by flash column chromatography on silica eluting with EtOAc:isohexane (3:2) to give a beige foam (79 mg, 46%). δ (¹H, 400 MHz, CDCl₃) 1.24-1.32 (2H, m), 1.63-1.72 (4H, m), 1.83-1.87 (2H, m), 2.27 30 (2H, t, J = 7.6 Hz), 2.43 (2H, t, J =), 2.60-2.70 (2H, m), 3.17 (2H, dd, J =

16.0 & 11.4 Hz), 3.42 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 4.45 (2H, d, J = 5.7 Hz), 4.70 (1H, Brs), 5.70 (1H, Brs), 6.99 (1 H, d, J = 8.2 Hz), 7.13-7.14 (2H, m), and 7.27-7.33 (5 H, m). (ES+) 574 ([MH]⁺).

5 Example 7



Step 1

A solution of 3-butyn-1-ol (5.0 ml, 77 mmol) in THF (20 ml) was added to a suspension of hexane-washed sodium hydride (3.7 g, 92.5 mmol) in THF (50 ml), under a nitrogen atmosphere at 0°C. The reaction was stirred at 0°C for 90 minutes before a solution of chloroacetonitrile (5.9 ml, 92.5 mmol) in THF (20 ml) was added dropwise. The black solution was stirred at 0°C for 15 minutes and at room temperature for 16 hours. The reaction was quenched by the careful addition of brine (150 ml) and the mixture was concentrated *in vacuo*. The residue was extracted with DCM (3 x 100 ml). The extracts were dried ($MgSO_4$) and evaporated *in vacuo* to a dark oil, which was purified by flash column chromatography on silica eluting with EtOAc:isohexane (1:9) to give 3-butyn-1-yloxyacetonitrile as a yellow liquid (777 mg, 9%). (ES+) 110 ([MH]⁺).

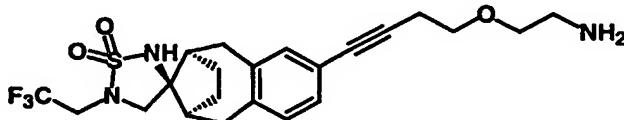
Step 2

A mixture of Intermediate 1 (508 mg, 1.0 mmol), the alkyne from Step 1 (218 mg, 2.0 mmol), tetrakis-triphenylphosphine palladium(0) (58 mg, 5 mol%), triphenyl phosphine (26 mg, 10 mol%) and copper iodide (20 mg, 10 mol%) in triethylamine (2 ml) and dioxane (2 ml) in a sealed tube, was purged with nitrogen and then heated at 100°C for 16 hours. The reaction was diluted with sodium hydrogen carbonate (sat, 20 ml) and extracted with ethyl acetate (2 x 20 ml). The extracts were washed with water (2 x 20 ml) and brine, dried ($MgSO_4$) and evaporated *in vacuo* to a brown gum, which was purified by flash column chromatography on silica eluting with EtOAc:isohexane (20 to 25 to 30%) to give a pale foam (354

mg, 76%). δ (^1H , 400 MHz, CDCl_3) 1.24-1.32 (2H, m), 1.68-1.72 (2H, m), 2.43 (2H, t, J = 7.0 Hz), 2.60-2.76 (4H, m), 3.18 (2H, dd, J = 16.0 & 8.2 Hz), 3.64-3.70 (2H, m), 3.79 (2H, t, J = 6.7 Hz), 4.33 (2H, s), 4.68 (1H, Brs), 7.00 (1 H, d, J = 8.2 Hz), and 7.16-7.18 (2H, m). (ES+) 468 ([MH] $^+$).

5

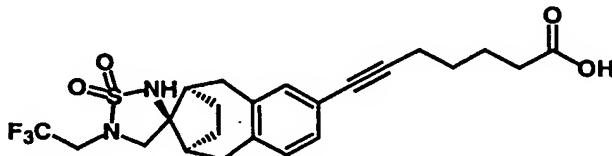
Example 8



Lithium aluminium hydride (1M in THF, 0.71 ml, 0.71 mmol) was added to a cold (0°C) solution of the nitrile from Example 7 Step 2 (330 mg, 0.71 mmol) in THF (10 ml) and the mixture was stirred at 0°C for 2 hours. The reaction was treated successively with water (28 μl), sodium hydroxide (28 μl) and water (84 μl) allowing 10 minutes between additions. The mixture was filtered through a bed of Celite® and washed through with THF. The filtrate was evaporated *in vacuo* to a gummy solid which was purified by SCX ion exchange resin eluting with ammonia (2M in methanol) to give after evaporation a pale yellow gum (195 mg, 58%). δ (^1H , 400 MHz, CDCl_3) 1.25-1.34 (2H, m), 1.67-1.71 (2H, m), 2.41-2.44 (2H, m), 2.60-2.71 (4H, m), 2.84-2.90 (2H, m), 3.17 (2H, dd, J = 16.0 & 8.2 Hz), 3.42 (2H, s), 3.48-3.50 (2H, m), 3.49-3.70 (4H, m), 7.00 (1 H, d, J = 8.2 Hz), and 7.15-7.17 (2H, m). (ES+) 472 ([MH] $^+$).

Example 9

25



A mixture of Intermediate 1 (100 mg, 0.2 mmol), 6-heptynoic (101 μl , 0.8 mmol), tetrakis-triphenylphosphine palladium(0) (12 mg, 5 mol%), triphenyl phosphine (5.2 mg, 10 mol%) and copper iodide (4 mg, 10 mol%)

in triethylamine (2 ml) and dioxane (2 ml) was purged with nitrogen and then heated at 100°C for 16 hours. The reaction was diluted with hydrochloric acid (1N) and extracted with ethyl acetate (2 x 25 ml). The extracts were washed with water (x 3) and brine, dried (MgSO_4) and 5 evaporated *in vacuo* to a yellow gum, which was purified by flash column chromatography on silica eluting with EtOAc:isohexane (1:3) to give a foam which was further purified by preparative TLC eluting with EtOAc:isohexane (1:3) to give a clear gum (11 mg, 12%). δ (^1H , 400 MHz, CDCl_3) 1.25-1.34 (2H, m), 1.57-1.84 (6H, m), 2.32-2.46 (8H, m), 2.55-2.69 10 (2H, m), 3.18 (2H, dd, J = 16.0 & 9.7 Hz), 3.42 (2H, s), 3.67 (2H, q, J = 8.7 Hz), 7.00 (1 H, d, J = 8.2 Hz), and 7.14-7.16 (2H, m). (ES+) 483 ([MH] \cdot).